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Allogeneic Stem Cell Transplantation for Myelodysplastic Syndrome Patients with a 5q Deletion

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A B S T R A C T

The deletion (5q) karyotype (del [5q]) in patients with myelodysplastic syndrome (MDS) is the most common karyotypic abnormality in de novo MDS. An increased number of blasts and additional karyotypic abnormalities (del [5q]+) are associated with a poor outcome. We analyzed the outcome of allogeneic hematopoietic cell transplants (HCT) in patients suffering from MDS with only del (5q) or del (5q)+ . A total of 162 patients, of median age 54 years (range, 9 to 73), having MDS and del (5q) abnormalities received HCT from identical siblings (n = 87) or unrelated donors (n = 75). The cumulative incidence of nonrelapse mortality and relapse incidence at 4 years was 29% (95% CI, 22 to 36) and 46% (95% CI, 38 to 54), whereas the estimated 4 year survival, relapse-free and overall, was 25% (95% CI, 18 to 33) and 30% (95% CI, 23 to 38), respectively. In a multivariate

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analysis patients with del (5q) and a blast excess displayed poorer survival (hazard ratio, 2.38; 95% CI, 1.44 to 3.93; $P < .001$), whereas female recipient sex resulted in improved survival (hazard ratio, .61; 95% CI, .41 to .90; $P = .01$). We conclude that allogeneic HCT can cure a subset of patients with MDS and a del (5q) abnormality.

INTRODUCTION

Myelodysplastic syndromes (MDS) are heterogeneous clonal hematopoietic stem cell malignancies characterized by ineffective hematopoiesis with peripheral blood cytopenia and a propensity to transform to acute leukemia [1]. However, the course of the disease is highly variable [2]. The World Health Organization proposed a cytologic classification [3] and revised it in 2008 [4]. The deletion (5q) karyotype (del [5q]) is the most common karyotypic abnormality in de novo MDS, occurring in approximately 10% to 20% of patients with MDS.

An increased number of blasts and additional karyotypic abnormalities (del [5q]+) are associated with a poorer prognosis [5]. Indeed, the outcome of patients with MDS is markedly affected by clonal chromosomal abnormalities [6,7]. These are taken into account in the International Prognostic Scoring System (IPSS), which in addition to the marrow blast count and peripheral blood cytopenia, considers 3 cytogenetic categories: patients with a normal karyotype, del (5q), del (20q), or -Y are classed as having a good risk, whereas patients with a complex karyotype (ie, >3 anomalies) or chromosome 7 abnormalities are considered to have a poor risk. All other chromosomal abnormalities are considered to carry an intermediate risk [8]. A revised version of the IPSS (R-IPSS) has been established that incorporates the blood transfusion requirements [9]. In the classic IPSS, del (5q), if associated with at least 2 other cytogenetic abnormalities, is classed as having a poor risk, whereas in the R-IPSS it is considered to carry a good risk in the absence of other cytogenetic abnormalities.

The 5q syndrome was first described in 1974 [10]. According to the World Health Organization classification it is a specific MDS subgroup [4]. This distinct syndrome occurs predominantly (>60%) in women and is associated with an isolated 5q deletion, erythroid hypoplasia, abnormal platelets, a relatively benign clinical course, and a probability of leukemic transformation of 10% to 20% [5].

The karyotype is a prognostic factor for survival in MDS and acute myeloid leukemia. In patients with (de novo) acute myeloid leukemia the loss of 5q often occurs in combination with additional chromosomal abnormalities and is generally considered to be a marker of high-risk disease [7]. Conversely, in MDS patients the 5q deletion is favorable. However, it is not known how the combination of del (5q) plus additional cytogenetic abnormalities and/or a blast excess affects the outcome of patients undergoing allogeneic stem cell transplantation. In this work we examined the impact, in MDS patients, of del (5q) as the only cytogenetic abnormality as compared with del (5q) in combination with other clonal anomalies ([5q]+), with regard to the prognosis after allogeneic hematopoietic cell transplantation (HCT). We investigated the outcome of this patient subpopulation retrospectively in the European Society for Blood and Marrow Transplantation (EBMT) registry.

METHODS

Patient Population

In the EBMT database we found 175 allografted MDS patients with a 5q deletion. Patients with a syngeneic (n = 1), matched other relative (n = 3), or mismatched relative (n = 9) graft were excluded, leaving a dataset of 162 individuals. Seventy-six patients had del (5q) as a single abnormality with (n = 37) or without (n = 39) blasts, whereas 86 had del (5q) plus another cytogenetic abnormality with (n = 71) or without (n = 15) blasts. The following variables were collected and analyzed: patient age at transplantation, interval between diagnosis and transplantation, type of donor (identical sibling or unrelated), source of stem cells (peripheral blood, bone marrow, or cord blood), cytogenetic data, and type of conditioning (reduced or standard intensity).

Type of Conditioning

Myeloablative conditioning comprised cyclophosphamide plus high-dose total body irradiation (>8 Gy) or cyclophosphamide plus high-dose busulfan (16 mg/kg total dose p.o. or the equivalent i.v. dose), with or without other high-dose cytotoxic agents and/or antithymocyte globulin or alemtuzumab. A reduced-intensity conditioning regimen comprised fludarabine plus intermediate doses of 1 or 2 alkylating agents or low-dose total body irradiation (2 Gy), with or without antithymocyte globulin or alemtuzumab. Intermediate doses of alkylating agents consisted of busulfan (8 to 10 mg/kg, p.o.), melphalan (80 to 140 mg/m^2, i.v.), cyclophosphamide (60 to 120 mg/m^2, i.v.), or thiotepa (5 to 10 mg/kg, i.v.).

Statistical Analyses

The primary endpoints were overall survival (OS), relapse-free survival (RFS), relapse incidence (RI), and nonrelapse mortality (NRM). OS was defined as the probability of survival after transplantation; death from any cause was considered an event. Patients alive at the time of the last follow-up were censored at this date. RFS was calculated as the time to death or relapse, whichever occurred first, patients surviving relapse-free being censored at the moment of the last follow-up. The probabilities of OS and RFS were estimated using the Kaplan-Meier product limit method, and differences between subgroups were assessed with the log-rank test.

RI was defined as the probability of relapse. NRM was defined as the probability of any death in the absence of relapse since HCT. For NRM and RI patients were censored if they were relapse-free and alive at the time of the last follow-up. The estimates of NRM and RI were calculated using cumulative incidence curves to accommodate competing risks (relapse was considered to be a competing risk for NRM and vice versa), whereas comparisons among subgroups were assessed using Gray's test. All follow-up times were censored at 4 years to allow valid comparisons between variables.

A Cox proportional hazards regression was used to assess the impact of potential prognostic factors on the multivariate analyses. The impact of these factors on OS, RFS, NRM, and RI was modeled by means of cause-specific hazards.

All *P*-values are 2-sided, and $P < .05$ was considered to be significant. All analyses were performed using software (R version 3.0.3) and the packages "prodlim" and "cmprsk".

RESULTS

Patient and Disease Characteristics

The demographic data of the study population are presented in Table 1. Seventy-six percent of the patients were aged ≥ 45 years, two-thirds had a bone marrow blast excess of >5%, and 47% had only del (5q). Among del (5q) patients with additional cytogenetic abnormalities, 78 (48%) fulfilled the criteria of complex karyotype. The IPSS score was low/intermediate-1 in 49% and 46% and intermediate-2/high in 51% and 54% at diagnosis and transplantation, respectively. Allogeneic stem cell transplantation was performed with cells from an identical sibling in 54% of patients, and the stem cell source was peripheral blood in 73%.

Outcome in the Whole Population

The percentage of engraftment was 92%. With a median follow-up of 68.2 months (95% confidence interval [CI], 59.3 to 85.0), at 4 years the NRM was 29% (95% CI, 22 to 36) and

Table 1
Patient and Disease Characteristics

Variable	No. of Patients	Percentage
Patient sex		
Male	68	42
Female	94	58
Donor sex		
Male	85	52
Female	77	48
Patient age, yr		
Median	54.6	
<45	39	24
≥45	123	76
Bone marrow blasts > 5%		
No	54	33
Yes	108	67
Additional cytogenetic abnormalities		
No	76	47
Yes	86	53
IPSS score (at diagnosis/transplantation)		
Low/intermediate-1	38/30	49/46
Intermediate-2/high	40/35	51/54
Stem cell source		
BM	34	21
PB	119	73
CB	9	6
Donor type		
Identical sibling	87	54
Unrelated	75	46
Recipient/donor CMV match		
−/−	44	30
−/+	20	14
+/−	28	19
+/+	55	37
Recipient/donor sex match		
Male/female	32	20
Other combinations	130	80
Del (5q) only		
Without blasts	37	23
With blasts	39	24
Del (5q) plus additional cytogenetic abnormalities		
Without blasts	15	9
With blasts	71	43

BM indicates bone marrow; PB, peripheral blood; CB, cord blood; CMV, cytomegalovirus.

the relapse rate 46% (95% CI, 38 to 54), resulting in a 4-year estimated OS of 30% (95% CI, 23 to 38) and RFS of 25% (95% CI, 18 to 33) (Figure 1).

The overall survival by excess of blasts is represented in Figure 2 and the relapse incidence and non relapse mortality by excess of blasts are represented in Figure 3.

Graft-versus-Host Disease

The incidences of acute (up to day 100) and chronic graft-versus-host disease (at 4 years starting from day 100) were 24.7% (95% CI, 17.8 to 31.5) and 44% (95% CI, 33 to 55), respectively. The incidence of grades I to II acute graft-versus-host disease was 12% and that of grades III to IV 13%. The incidences of limited and extended chronic graft-versus-host disease were 33% and 10%, respectively.

Univariate and Multivariate Analyses

Univariate analyses

In terms of OS at 4 years, the results were better for those without excess of blast, an IPSS at diagnosis low or intermediate-1, and there was a trend in favor of patients younger than age 45 years. All other factors had no impact on survival: presence or not of additional cytogenetic abnormalities, type of conditioning regimen, donor type, stem cell source, recipient–donor cytomegalovirus match, recipient–donor sex match, and the time from diagnosis to transplantation (< or >12 months) (Table 2).

Multivariate analysis

All factors found to be significant in the univariate analyses were included in the multivariate analysis (Table 2). In a multivariate Cox regression analysis the recipient–donor gender match, recipient–donor cytomegalovirus status, and interval between diagnosis and treatment did not influence the outcome.

OS was influenced by the presence of an excess of blasts (hazard ratio [HR], 2.38; 95% CI, 1.44 to 3.93; $P < .001$), whereas female recipients had a more favorable outcome as compared with males (HR, .61; 95% CI, .41 to .90; $P = .01$). A significant trend was found for the age category ≥ 45 years (versus <45 years) (HR, 1.57; 95% CI, .94 to 2.63; $P = .09$). The presence of additional cytogenetic abnormalities did not significantly affect OS (HR, 1.07; 95% CI, .70 to 1.63; $P = .76$) (Table 3).

RFS was influenced by an excess of blasts (HR, 2.02; 95% CI, 1.26 to 3.24; $P < .001$), whereas the gender of the recipient displayed a significant trend in favor of women (HR, .69; 95% CI, 1.009 to .056; $P = .056$). Additional cytogenetic abnormalities and age category were not significantly associated with RFS.

Concerning the incidence of relapse, an excess of blasts (HR, 2.24; 95% CI, 1.15 to 4.38; $P = .02$ and additional cytogenetic abnormalities (HR, 1.84; 95% CI, 1.03 to 3.29; $P = .04$) had significant influence, whereas the type of donor was almost significant, with a more favorable outcome for unrelated donors (versus identical siblings) (HR, .62; 95% CI, .37 to 1.02; $P = .06$). Finally, for NRM only the type of donor was a significant factor, with unrelated donors being less favorable (versus identical siblings) (HR, 1.80; 95% CI, 1.09 to 3.31; $P = .02$).

DISCUSSION

MDS comprises a wide range of different diseases displaying various prognoses. Except for the del (5q) syndrome, which has a better prognosis, the outcome may be dismal. The R-IPSS score has greatly improved our capacity to predict survival, and the chromosomal abnormality del (5q) is considered to be a good feature. However, the impact of a 5q deletion plus additional abnormal cytogenetics is not really known.

Patients with low-risk MDS can benefit from supportive care for a long time, but eventually they will become transfusion dependent and some will progress to acute leukemia. The lag time between diagnosis and transformation to acute leukemia is much shorter for high-risk MDS patients. In our study the interval between diagnosis and treatment did not influence the outcome.

Allogeneic stem cell transplantation is an established curative option for most patients with advanced stages of MDS. Conversely, only some patients with low-risk MDS are considered for treatment by allogeneic HCT. The main reason for this restrictive approach is the high incidence of procedure-related mortality, which was as high as 50% to 60% in some studies on patients transplanted before 1996 [11]. Nevertheless, the populations selected for allogeneic HCT usually include a high proportion of patients with poor-risk characteristics, such as adverse cytogenetic abnormalities, therapy-related MDS, high transfusion requirements, marrow

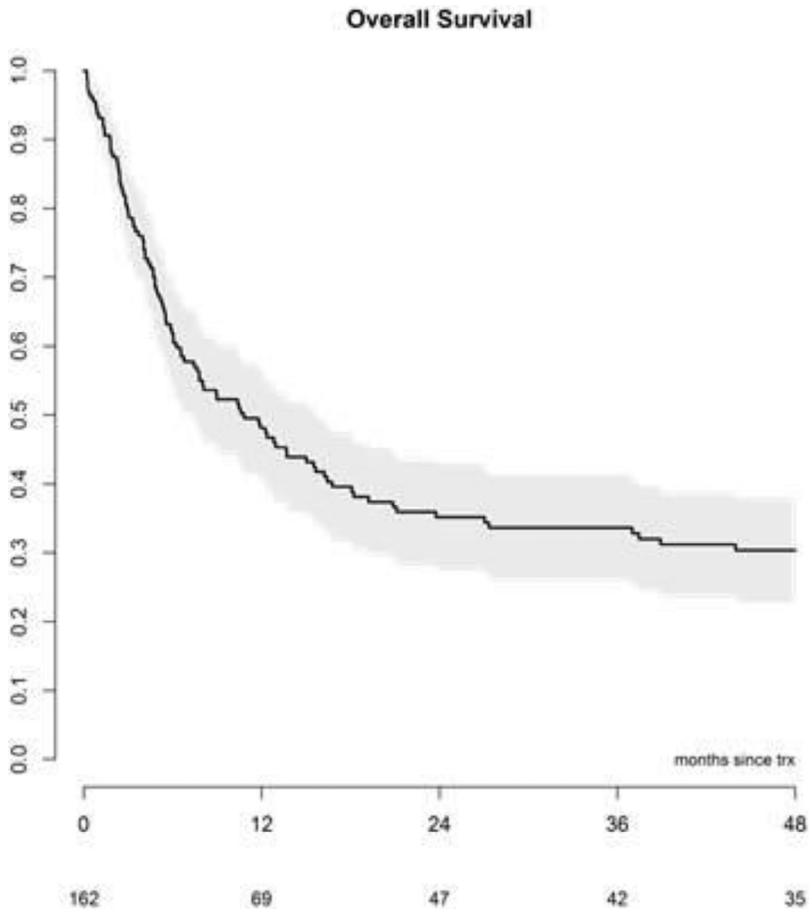

Figure 1. OS after allogeneic stem cell transplantation in patients with a del (5q) karyotype.

fibrosis, profound cytopenia, or a poor response to treatment [12].

This retrospective, EBMT registry-based study included 162 patients with MDS and del (5q). An excess of blasts, but not additional cytogenetic abnormalities, had a major impact on the outcome. With no excess of blasts the OS at 4 years was 53%, as compared with only 21% in the presence of more than 5% blasts. Women had a better prognosis, whereas there was a trend to an improved outcome in patients younger than age 45 years.

The outcome of allogeneic HCT in patients with MDS and a del (5q) karyotype was reported in a retrospective British study [13]. The major prognostic factor was likewise the blast count, but, unlike in our work, additional cytogenetic abnormalities had a negative impact. Cytogenetic abnormalities are highly predictive of the outcome after allogeneic bone marrow transplantation in advanced stages of MDS [14-16]. However, in another study the presence of cytogenetic abnormalities in patients with early stages of MDS (refractory anemia or refractory anemia with ring sideroblast) did not influence the outcome of allogeneic HCT [17].

We found a better OS for female patients and a trend toward improved OS for younger ones. The influence of age on the survival of MDS patients has already been described [18], with a better survival for patients younger than age 50 years. In contrast, the influence of sex remains under

Table 2
Univariate Analysis

	OS	NRM	RI
Excess of blasts: yes vs. no	21% vs. 53% ($P < .001$)	29% vs. 27% ($P = .75$)	54% vs. 25% ($P = .001$)
Cytogenetics abnormalities: yes vs. no	26% vs. 36% ($P = .24$)	26% vs. 33% ($P = .44$)	59% vs. 29% ($P = .001$)
Conditioning regimen: reduced vs. standard	29% vs. 32% ($P = .59$)	29% vs. 28% ($P = .82$)	44% vs. 47% ($P = .76$)
Donor type: unrelated vs. identical sibling	30% vs. 30% ($P = .81$)	37% vs. 22% ($P = .05$)	35% vs. 54% ($P = .03$)
Stem cell source: marrow vs. PB vs. CB	29% vs. 31% vs. 22% ($P = .31$)	30% vs. 27% vs. 44% ($P = .43$)	42% vs. 48% vs. 33% ($P = .72$)
IPSS at diagnosis: low/intermediate-1 vs. intermediate-2/high	42% vs. 14% ($P < .001$)	24% vs. 43% ($P = .09$)	38% vs. 49% ($P = .30$)
Age: >45 yr vs. <45 yr	25% vs. 46% ($P = .06$)	29% vs. 27% ($P = .80$)	47% vs. 42% ($P = .42$)
CMV match: R–/D– vs. R–/D+ vs. R+/D– vs. R+/D+	31% vs. 27% vs. 24% vs. 37% ($P = .63$)	24% vs. 22% vs. 37% vs. 29% ($P = .54$)	55% vs. 65% vs. 38% vs. 35% ($P = .21$)
Donor/recipient match: female D/male R vs. other	22% vs. 32% ($P = .38$)	31% vs. 28% ($P = .93$)	50% vs. 45% ($P = .41$)
Time diagnosis to transplantation: >12 mo vs. ≤12 mo	38% vs. 25% ($P = .11$)	28% vs. 29% ($P = .84$)	48% vs. 43% ($P = .41$)

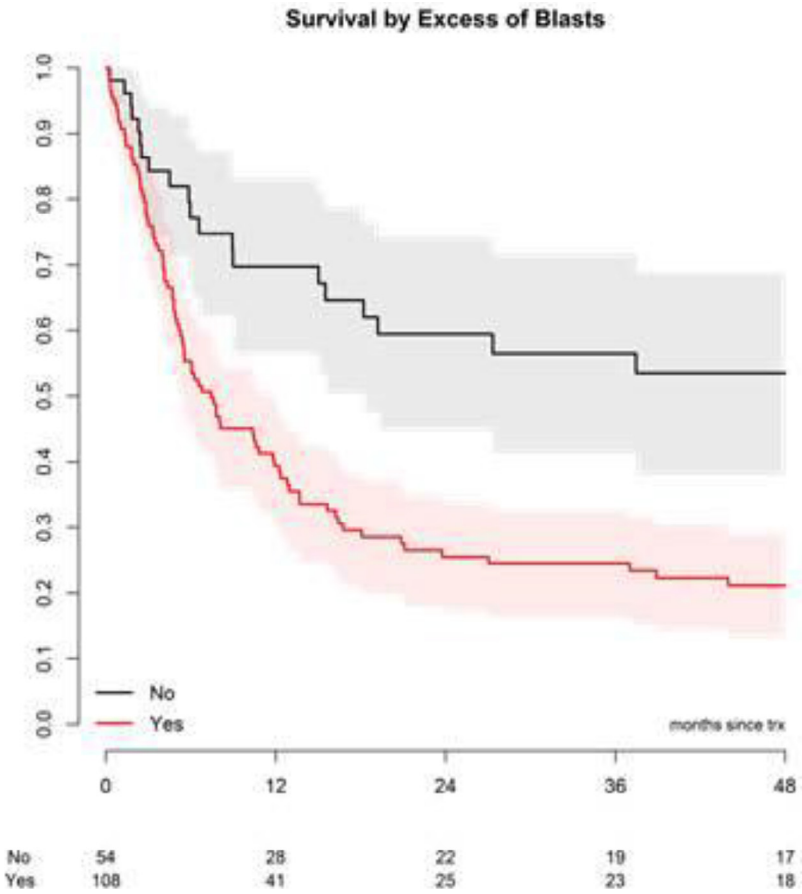

Figure 2. OS survival after allogeneic stem cell transplantation in patients with a del (5q) karyotype, with or without an excess of blasts.

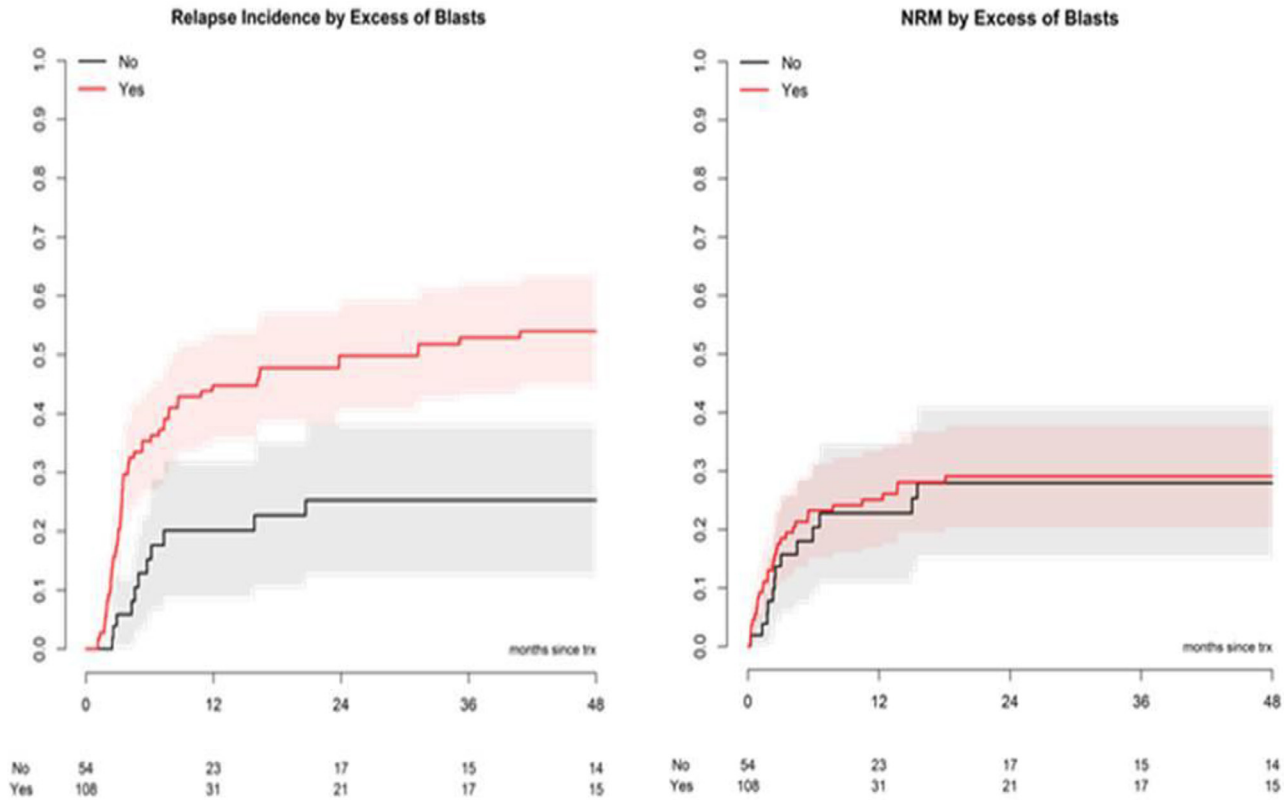

Figure 3. RI and NRM after allogeneic stem cell transplantation in patients with a del (5q) karyotype, with or without an excess of blasts.

Table 3
Multivariate Cox Regression Models for OS, RFS, Relapse, and NRM

Variable	HR	Lower 95% CI	Upper 95% CI	*P*
OS				
Marrow blasts > 5%				
No	1			
Yes	2.38	1.44	3.93	<.001
Additional cytogenetic abnormalities				
No	1			
Yes	1.07	.70	1.63	.76
Recipient sex				
Male	1			
Female	.61	.41	.90	.01
Age category, yr				
<45	1			
≥45	1.57	.94	2.63	.09
RFS				
Marrow blasts > 5%				
No	1			
Yes	2.02	1.26	3.24	<.001
Additional cytogenetic abnormalities				
No	1			
Yes	1.36	.9	2.06	.14
Recipient sex				
Male	1			
Female	.69	.47	1.009	.056
Age category, yr				
<45	1			
≥45	1.33	.84	2.11	.22
Relapse				
Marrow blasts > 5%				
No	1			
Yes	2.24	1.15	4.38	.02
Additional cytogenetic abnormalities				
No	1			
Yes	1.84	1.03	3.29	.04
Donor relationship				
Identical sibling	1			
Unrelated	.62	.37	1.02	.06
NRM				
Marrow blasts > 5%				
No	1			
Yes	1.30	.67	2.55	.44
Additional cytogenetic abnormalities				
No	1			
Yes	.77	.43	1.41	.38
Donor relationship				
Identical sibling	1			
Unrelated	1.80	1.09	3.31	.02

discussion, particularly in low-risk MDS patients [19]. In these patients we found a significant effect of age and sex on survival in the univariate models, whereas the multivariate model confirmed this effect only for age. Another study concluded that age and sex and their interaction could influence the prognostication of patients, but only when using the IPSS rating [20]. A further study demonstrated that this impact on the prognosis of del (5q) MDS patients was not only due to age and sex, although more advanced age and male sex were important risk factors, but the World Health Organization classification subtypes also played a role [21]. In the allogeneic setting, age has previously been identified as an important prognostic factor [22].

Patients with 5q syndrome respond well to lenalidomide. Thus, a reduced need for transfusion was reported in 76% of patients with 67% no longer requiring transfusion, regardless of the karyotype complexity, whereas 45% displayed a complete cytogenetic response [23]. However, no cure was observed, and the median duration of response was approximately 2 years. Acute myeloid leukemia transformation occurred in 15% to 21% of patients showing a cytogenetic response and in 60% to 67% of nonresponding patients [24-26]. Unfortunately, data on lenalidomide treatment before transplantation were not available for our study.

Recently, TP53 mutations were described as a predictor of progression in low-risk MDS with del (5q) [27,28]. It was suggested that the mutated subclone might be insensitive to lenalidomide and gradually progress, despite a strong inhibitory effect on the total proportion of cells carrying del (5q), leading to transient partial cytogenetic remission. The presence of clinically relevant subclones with mutations such as TP53 could lead to genetic instability and disease progression. However, the p53 mutation has also been described as a poor prognostic factor after allogeneic stem cell transplantation [29]. In these 2 scenarios patients who do not respond to lenalidomide and those harboring the TP53 mutation need more aggressive treatment, and allogeneic HCT could be an option. Indeed, genetic mutations help to predict clinical outcomes after allogeneic HCT [30].

There are several limitations to our study. First, the number of patients was relatively small. Second, patients were transplanted over a period of several years, and investigators did not know why particular del (5q) MDS patients were selected for transplantation. Also, the R-IPSS scores were missing. Nonetheless, the data presented here shed light on the expected outcome of HCT in patients with this particular subtype of MDS.

In summary, MDS patients with cytogenetic abnormalities including a 5q deletion but without excess blasts can achieve a good outcome when treated by allogeneic stem cell transplantation, reaching in our study 50% OS at 4 years. These findings suggest that patients with del (5q) should be transplanted early in the course of their disease, before a rising blast count indicates disease evolution. How should allogeneic stem cell transplantation be used in patients with MDS and del (5q)? Lenalidomide has become an approved and reasonable treatment option that enables a remarkable reduction in the frequency of transfusion. However, elegant laboratory experiments suggest that lenalidomide does not target the stem cell population in del (5q) MDS patients [31]. Eligible patients with an increasing number of blasts and del (5q) MDS should be considered for allogeneic stem cell transplantation, as likewise patients who do not or no longer respond to lenalidomide.

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